REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on July 3, 2002. Claims 5, 6 and 20-29 have been cancelled herein without prejudice to further prosecution in a continuation application. Claims 60-67 have been added herein. Support for the newly added claims can be found, for example, at pages 2, 3, and 25. Claims 1 and 4-19, 30, and 60-67 are pending. Claims 1 and 4-30 have been rejected.

A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims, and any other claims supported by the specification, in the future. The comments in the Office action are now addressed in turn.

Rejections under 35 U.S.C. §112

Claims 1, 4-12, 15, 17, 20, 21, 23, 26, and 27 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and claim the invention. Applicants respectfully traverse this rejection.

More specifically, the Examiner has expressed concerns regarding the definition of R^4. The claims recite " substituted alkyl" or "substituted lower alkyl" as well as "R_{16}-alkylene". The Office states that a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite. Applicants have amended the claims herein to address the Examiner's concerns. Applicants request that the rejection be withdrawn.

The Office also has expressed concern regarding the antecedent basis of Claim 12. Applicants respectfully traverse this rejection.

Specifically, Applicants note that the Specification at page 10 states:

> Lower alkyl refers to alkyl groups of from 1 to 5 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like.

As such, "butoxy" as used in Claim 12 is a lower alkyl (or more specifically, a lower alkoxy) as recited in Claim 11. Thus, the antecedent basis is correct. Applicants request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-10, 13, 14, and 30 have been rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Padia U.S. Patent No. 5,756,502 ("Padia") in view of Aono et al. U.S. Patent No. 5,753,664 ("Aono"). Claims 1, 23, and 30 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over Pattanaik et al. (1998) Ind. J. Chem. 37:1304-1306 ("Pattanaik") in view of Aono. Finally, Claims 1 and 4-30 have been rejected under 35 U.S.C. §103(a) as being unpatentable over the "list of purchased compounds" in view of Aono. Applicants respectfully traverse this rejection.

The Present Invention

The present invention is directed to methods of utilizing a novel class of compounds having a core quinazolinone structure that are modulators of mitotic kinesins, and more particularly, modulators of the mitotic kinesin KSP. Applicants have amended the claims herein to focus on one of the preferred embodiments of the present invention, namely, methods of treating cellular proliferative diseases comprising the administration of a quinazolinone amides of formula 1(a). The compounds used in the claimed methods have been defined by quite specific substituents at the various R groups. In addition, each of the compounds used in the claimed methods have a sidechain that is a tertiary amide, i.e., the amide nitrogen does not bear a hydrogen group.

As is detailed in the Specification at Examples 4-8 and at pages 47-48 and Figure 3, compounds within these classes have been shown to inhibit cell proliferation with GI_{50} values well within the range of anti-proliferative agents used in the clinic. These compounds can be used, for example, to inhibit human KSP; to treat diseases of proliferating cells; to develop inhibitors and modulators of KSP; and the like.

Padia in view of Aono

Padia U.S. Patent No. 5,756,502 ("Padia") is cited for its teaching of Examples 4 and 7. Applicants note that none of the compounds cited by the Examiner have a stereogenic center as is in the compounds used in the methods claimed herein. Moreover, the R_4 group in each of the other cited compounds (according to the nomenclature of the specification) is hydrogen rather that the groups claimed herein. In other words, the cited compounds are not tertiary amides as claimed herein. In addition, Padia does not teach or suggest the claimed compositions or methods for their use.

Aono is cited for its description of a a genus of compounds that inhibit cell growth and have antitumor activity. The Examiner argues that Aono would have provided sufficient motivation for one skilled in the art to use some of the claimed compounds in the treatment of cellular proliferative disease.

Applicants respectfully disagree in that Aono does not rectify the deficiencies of Padia. Neither reference, either alone or in combination, teaches or suggests the use of quinazolines as recited in the claimed methods. As such, Applicants respectfully request that the rejection be withdrawn.

Pattanaik in view of Aono

Claims 1, 23, and 30 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pattanaik et al. (1998) Ind. J. Chem. 37:1304-1306 ("Pattanaik") in view of Aono. Pattanaik is said to describe compounds in Table I that are embraced by the last formula in Claim 1. Applicants note that the last formula in Claim 1 has been cancelled herein. As the rejection is moot, Applicants request that it be withdrawn.

List in view of Aono

The Examiner has rejected the claims under 35 U.S.C. §103(a) as being unpatentable over the "list of purchased compounds" in view of Aono. Because Aono allegedly relates substituted quinazolinone compounds to antitumor activity, the Office maintains that one skilled in the art would have been motivated to treat cellular proliferative disease using the claimed compounds. Applicants respectfully disagree and traverse this rejection.

Aono describes ketones of the formula:

$$A—Z—Ar^1—CO—Ar^2$$

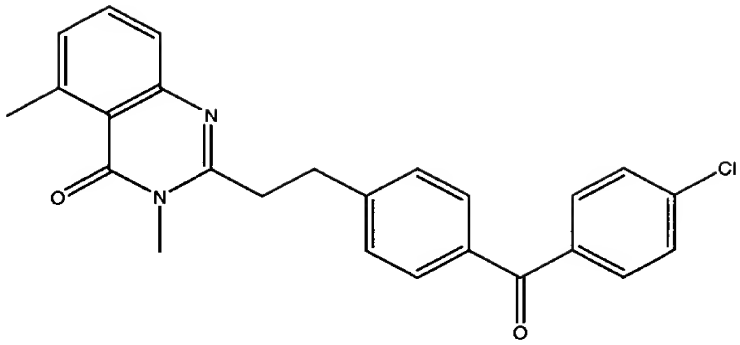
wherein ring A is an optionally substituted condensed pyrimidinone or condensed pyridazinone ring; Ar^1 and Ar^2 are independently an optionally substituted ring; Z is a divalent group, or salts thereof. Aono further describes *55* different subclasses of compounds falling within the broad genus.

In one of these 55 embodiments, Ring A is described as: an optionally substituted pyrrolo[2,3-d]pyrimidin-4-one, pyrrolo[3,2-d]pyrimidin-4-one, pyrrolo[3,4-d]pyrimidin-4-one, pyrazolo[3,4-d]pyrimidin-4-one, pyrazolo[4,3-d]pyrimidin-7-one, 6-oxopurine, imidazo[1,2-a]pyrimidin-5-one, imidazo[1,2-a]pyrimidin-7-one, thieno[2,3-d]pyrimidin-4-one, thieno[3,4-

d]pyrimidin-4-one, thieno[3,2-d]pyrimidin-4-one, furo[2,3-d]pyrimidin-4-one, furo[3,4-d]pyrimidin-4-one, furo[3,2-d]pyrimidin-4-one, isoxazolo[5,4-d]pyrimidin-4-one, isoxazolo[4,5-d]pyrimidin-7-one, oxazolo[5,4-d]pyrimidin-4-one, oxazolo[4,5-d]pyrimidin-7-one, thiazolo[5,4-d]pyrimidin-4-one, thiazolo[4,5-d]pyrimidin-7-one, isothiazolo[5,4-d]pyrimidin-4-one, isothiazolo[4,5-d]pyrimidin-7-one, triazolo[4,5-d]pyrimidin-4-one, 1,2,4-triazolo[1,5-a]pyrimidin-7-one, dihydrocyclopenta[d]pyrimidin-4-one, 5H- or 7H-cyclopenta[d]pyrimidin-4-one, pyrido[2,3-d]pyrimidin-4-one, pyrido[3,2-d]pyrimidin-4-one, pyrido[4,3-d]pyrimidin-4-one, pyrido[3,4-d]pyrimidin-4-one, pteridin-4-one, quinazolin-4-one, pyrido[1,2-a]pyrimidin-4-one, pyrimido[1,2-a]pyrimidin-4-one, thiazolo[3,2-a]pyrimidin-5-one, oxazolo[3,2-a]pyrimidin-5-one, pyrrolo[1,2-a]pyrimidin-4-one, pyrimido[3,4-a]pyrimidin-4-one, pyrimido[4,5-d]pyrimidin-4-one, pyrimido[5,4-d]pyrimidin-4-one, pyridazino[2,3-a]pyrimidin-4-one, pyridazino[4,3-d]pyrimidin-4-one, pyridazino[3,4-d]pyrimidin-4-one, xanthine, uric acid, pyrrolo[3,2-d]pyrimidin-2,4-dione, pyrrolo[2,3-d]pyrimidin-2,4-dione, pyrrolo[3,4-d]pyrimidin-2,4-dione, pyrimido[2,1-b][1,3]thiazin-6-one, pyrimido[2,1-b][1,3]oxazin-6-one, imidazo[2,1-b]quinazolin-5-one, cyclopento[d]imidazo[1,2-a]pyrimidin-5-one, cyclopento[d]imidazo[1,2-a]pyrimidin-5-one, pyridazino[4,5-b]-1,5-oxazepin-9(8H)-one, pyridazino[4,5-b]-1,4-oxazin-8(7H)-one, pyrrolo[3,4-d]pyridazin-4(5H)-one, pyrrolo[2,3-d]pyridazin-7(6H)-one, pyrrolo[2,3-d]pyridazin-4(5H)-one, imidazo[4,5-d]pyridazin-4(5H)-one, imidazo[4,5-c]pyridazin-4(5H)-one, pyrazolo[4,3-d]pyridazin-4(5H)-one, pyrazolo[3,4-d]pyridazin-4(5H)-one, triazolo[4,5-d]pyridazin-4(5H)-one, pyrido[2,3-d]pyridazin-5(6H)-one or thiazolo[4,5-d]pyridazin-7(6H)-one.

Moreover, Aono describes the synthesis of a variety of quinazolinones. These quinazolinones have an oxy, thio, or vinyl substituent off of the quinazolinone core or have a fused ring system linking the two ring nitrogens of the quinazolinone core. As such, they do not fall within the scope of the claimed methods.

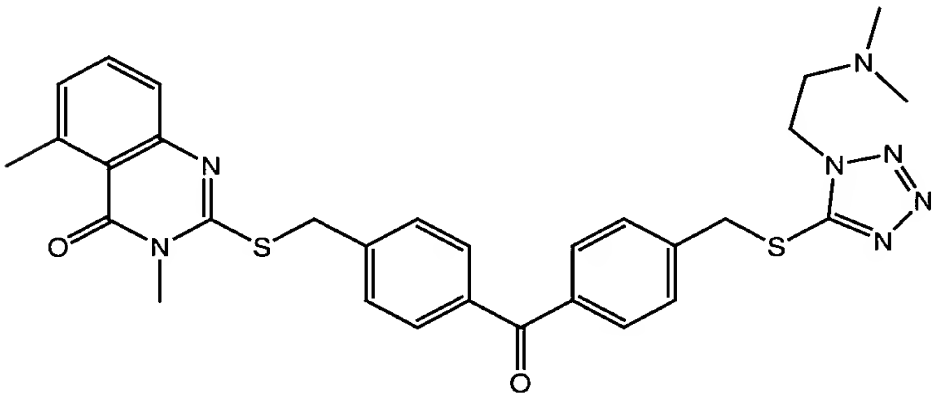
Aono also describes the synthesis of several compounds having a $-(CH_2CH_2)-$ group appended to the quinazolinone core. For example, Example 262 describes the synthesis of:



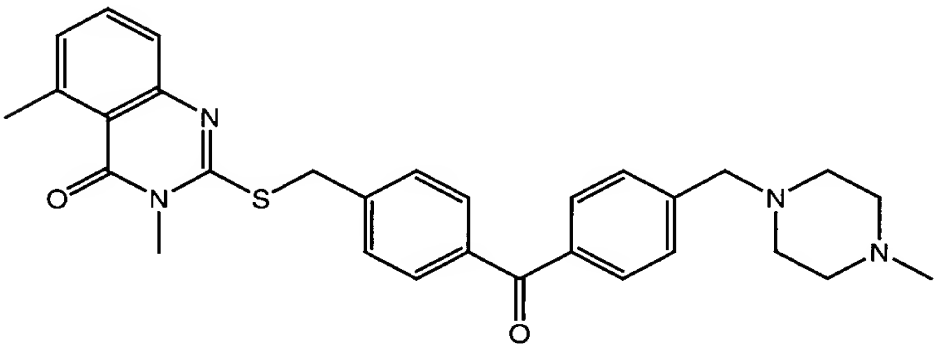
See, also Examples 264, 266, 267, and 270. As none of these compounds have the requisite amide substitution off of the quinazolinone core, they do not teach or suggest the compounds used in the claimed methods.

Finally, Aono describes the synthesis of over 400 compounds. None of these compounds are embraced within the scope of the compounds used in the claimed methods. Moreover, the only quinazolinones reported in Aono with specific biological activity are the following

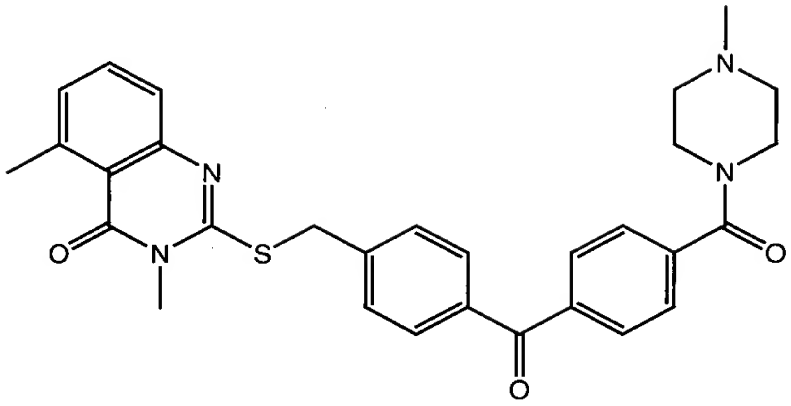
Example 138



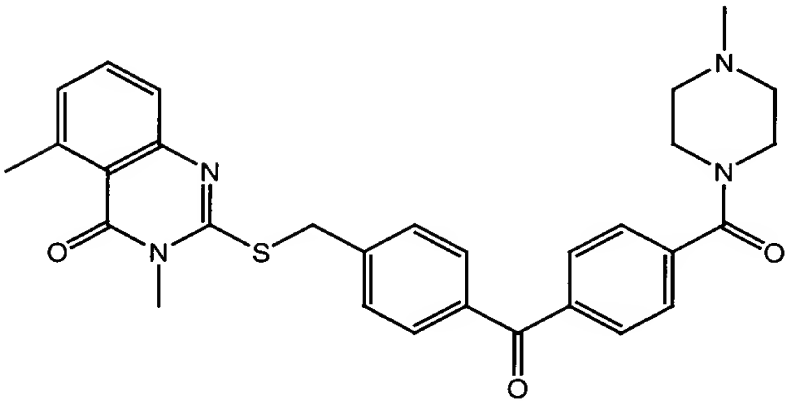
Example 144



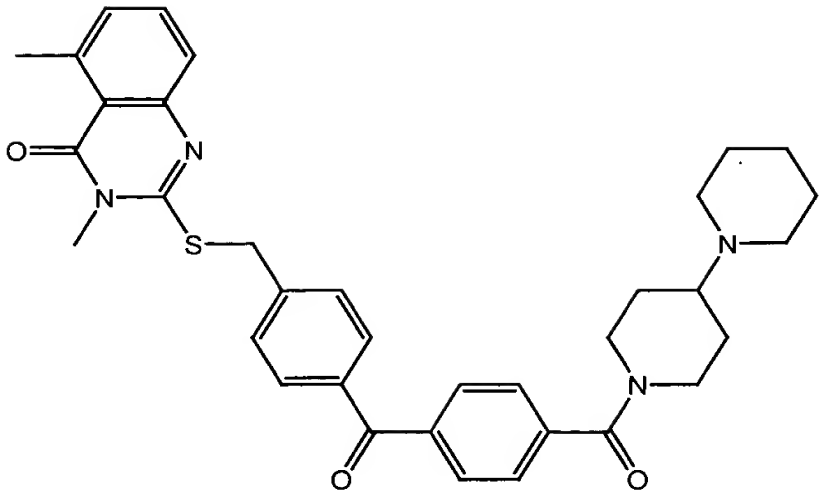
Example 184



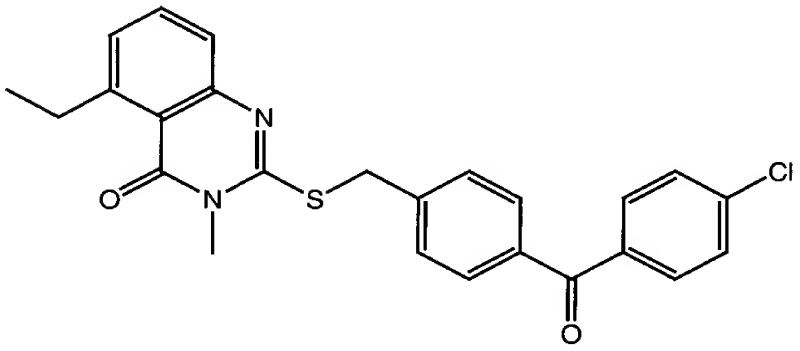
Example 189



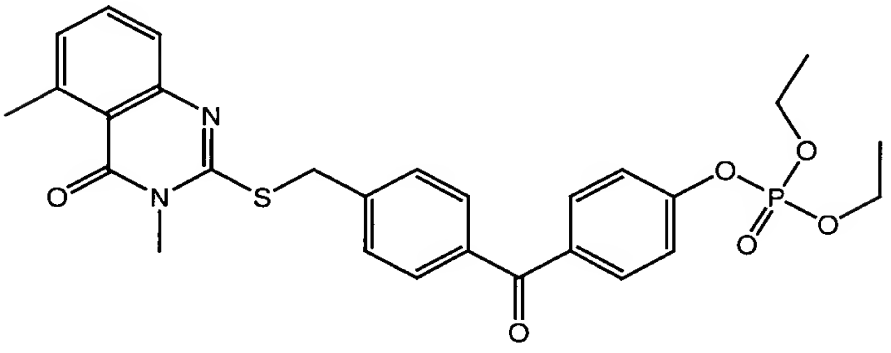
Example 193



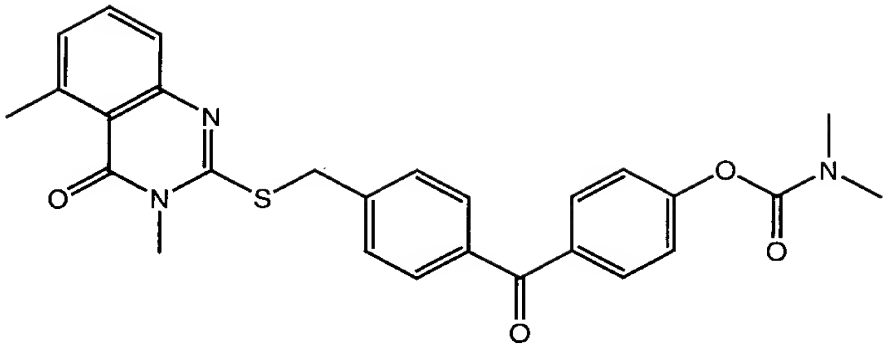
Example 214



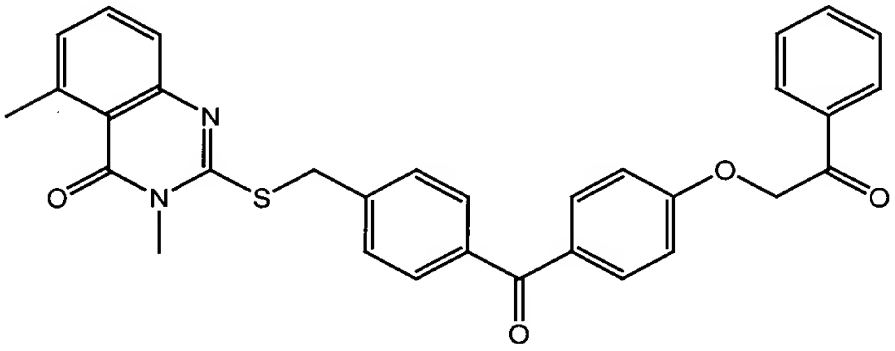
Example 217



Example 228



Example 234



Example 329

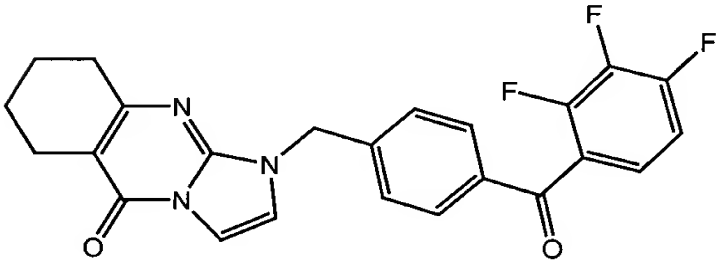


Table 2 - Example 42

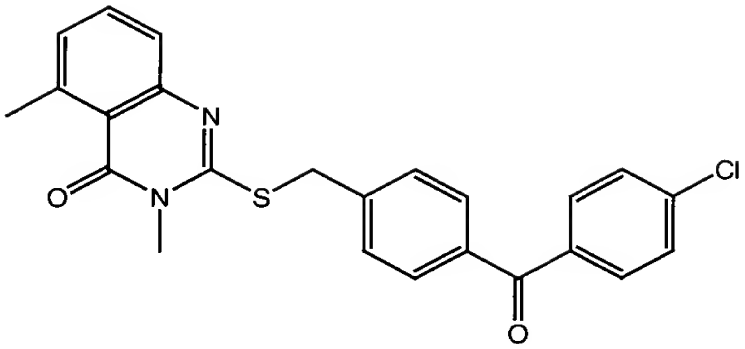
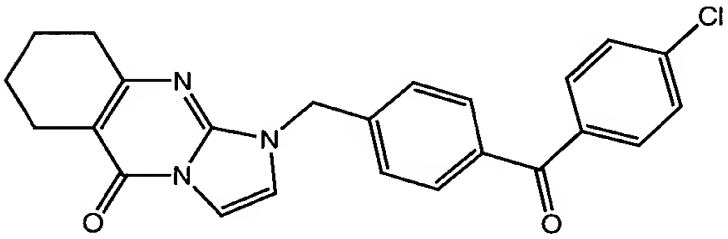


Table 3 - Example 189



Each of the above compounds has either a fused ring or a thio substituent off of the quinazolinone core. Applicants respectfully maintain that Aono does not teach or suggest that the compounds used in the claimed methods – compounds that have an amide side chain – would be useful in the treatment of cellular proliferative disease.

Applicants assert that by suggesting that the cited art may be used to produce the presently claimed invention, the Examiner presents, in essence, an "obvious to experiment" or "obvious to try" standard for obviousness. The "obvious to try" standard has been thoroughly discredited by the courts. Indeed, an obviousness rejection is *inappropriate*, where the prior art gives no indication of which parameters are critical or no direction as to which of many choices is likely to be successful. *In re O'Farrell*, 7 USPQ2d 1673, 1681 Fed. Cir. 1988. "Both the suggestion and the expectation of success must be founded in the prior art, and not in applicant's disclosure." *In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Applicants respectfully maintain that there is simply no suggestion in the cited references that a quinazolinone having an amide sidechain would be useful for the treatment of cellular

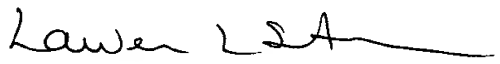
proliferative disease. Thus, there is nothing in the cited prior art that would provide one of ordinary skill in the art with the knowledge necessary to develop the claimed inventions.

Applicants respectfully submit that the claimed invention is not obvious from the cited references. Applicants request that the rejection be withdrawn.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP



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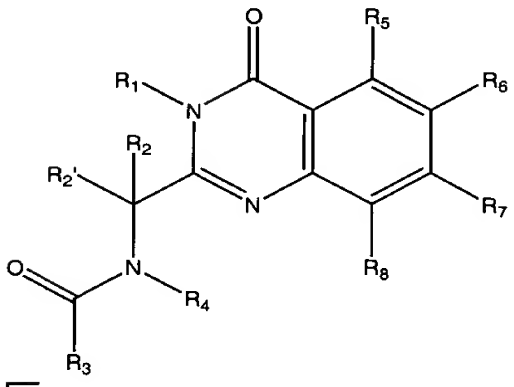
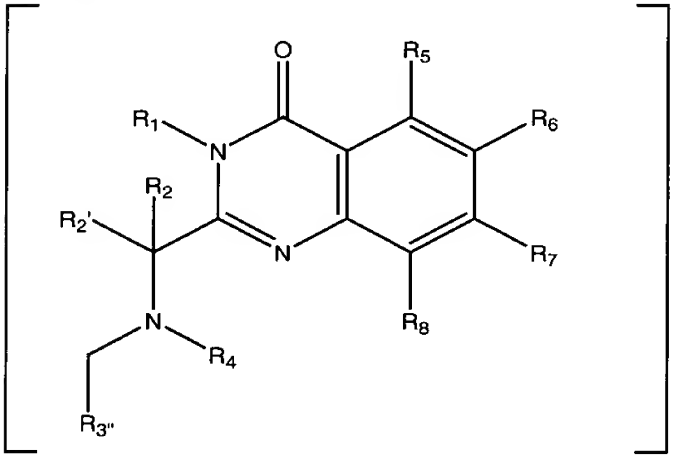
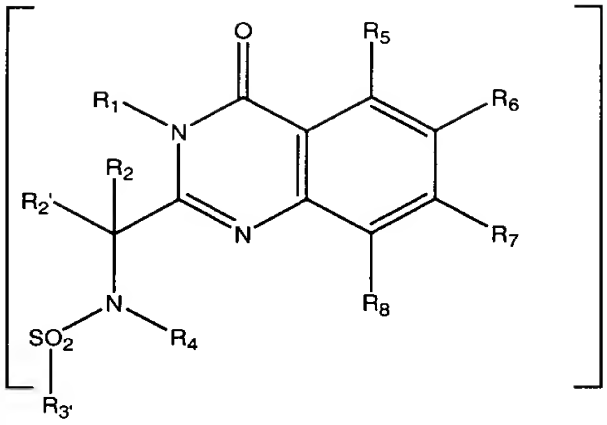
MARKED UP VERSION OF AMENDED CLAIMS

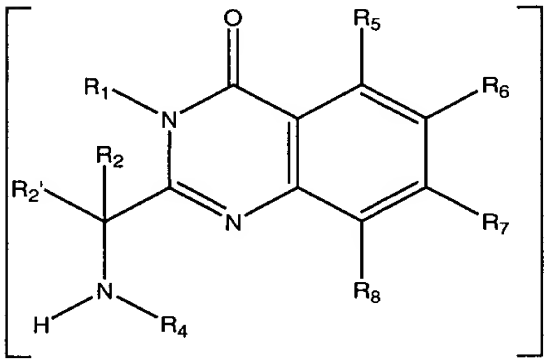
1. (Amended) A method of treating cellular proliferative diseases comprising administering a compound chosen from the group consisting of:







[and]



wherein:

R_1 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_2 and R_2' are independently chosen from hydrogen, alkyl, oxaalkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl; or R_2 and R_2' taken together form a 3- to 7-membered ring;

R_3 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, oxaalkyl, oxaalkylaryl, substituted oxaalkylaryl, $R_{15}O$- and R_{15}-NH-;

[$R_{3'}$ is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, and R_{15}-NH-;

$R_{3''}$ is chosen from alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_4 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, and R_{16}-alkylene-] <u>R_4 is chosen from alkyl, aryl, alkylaryl, alkylheteroaryl, substituted alkyl, and substituted aryl</u>;

R_5, R_6, R_7 and R_8 are independently chosen from hydrogen, alkyl, alkoxy, halogen, fluoroalkyl, nitro, dialkylamino, alkylsulfonyl, alkylsulfonamido, sulfonamidoalkyl, sulfonamidoaryl, alkylthio, carboxyalkyl, carboxamido, aminocarbonyl, aryl and heteroaryl; **<u>and</u>**

R_{15} is chosen from alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

[R_{16} is chosen from alkoxy, amino, alkylamino, dialkylamino, N-heterocyclyl and substituted N-heterocyclyl,]

<u>or a pharmaceutically acceptable salt of any of the foregoing compounds</u>.

4. (Twice amended) A method according to claim 1 wherein

R_1 is chosen from hydrogen, alkyl, aryl, substituted alkyl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl and substituted alkylheteroaryl;

R_2 is chosen from hydrogen, alkyl and substituted alkyl;

R_2' is hydrogen;

R_3 is chosen from alkyl, substituted alkyl, alkylaryl, heteroaryl, aryl, substituted aryl, substituted hereroaryl, substituted oxaalkylaryl $R_{15}O$- and R_{15}-NH-;

R_4 is chosen from alkyl, aryl, alkylaryl, alkylheteroaryl, substituted alkyl, **<u>and</u>** substituted aryl[, and R_{16}-alkylene-];

R_5 is hydrogen;

R_6, R_7 and R_8 are independently chosen from hydrogen, halogen, methyl and trifluoromethyl; **<u>and</u>**

R_{15} is chosen from alkyl, aryl and substituted aryl**[;**

R_{16} is chosen from alkoxy, amino, alkylamino, dialkylamino and N-heterocyclyl].

7. (Amended) A method according to claim [6] **<u>4</u>** wherein R_1 is chosen from hydrogen, lower alkyl, substituted lower alkyl, benzyl, substituted benzyl, phenyl, naphthyl and substituted phenyl.

9. (Amended) A method according to claim [6] **4** wherein R_2 is chosen from hydrogen, lower alkyl and substituted lower alkyl, and R_2' is hydrogen.

11. (Amended) A method according to claim [6] **4** wherein R_3 is chosen from C_1-C_{13} alkyl; substituted lower alkyl; phenyl; naphthyl; phenyl substituted with one or more halo, lower alkyl, loweralkoxy, nitro, carboxy, methylenedioxy or trifluoromethyl; biphenylyl; benzyl; phenoxymethyl; halophenoxymethyl; phenylvinyl; heteroaryl; heteroaryl substituted with lower alkyl; and benzyloxymethyl.

13. (Amended) A method according to claim [6] **4** wherein R_3 is R_{15}-NH- and R_{15} is chosen from lower alkyl; cyclohexyl; phenyl; and phenyl substituted with halo, lower alkyl, loweralkoxy, or lower alkylthio.

15. (Amended) A method according to claim [6] **4** wherein R_4 is chosen from lower alkyl, substituted lower alkyl, cyclohexyl; phenyl substituted with hydroxy, lower alkoxy or lower alkyl; benzyl; heteroarylmethyl; heteroarylethyl; **and** heteroarylpropyl **[and R_{16}-alkylene-, wherein R_{16} is amino, lower alkylamino, di(lower alkyl)amino, lower alkoxy, or N-heterocyclyl].**

17. (Amended) A method according to claim [6] **4** wherein
R_1 is chosen from lower alkyl, benzyl, substituted benzyl and substituted phenyl;
R_2 is chosen from hydrogen, alkyl, substituted lower alkyl and benzyl;
R_2' is hydrogen;
R_3 is chosen from substituted phenyl and naphthyl;
R_4 is **[chosen from]** substituted alkyl **[and R_{16}-alkylene-];**
R_5 is hydrogen or halo
R_6 is hydrogen, methyl or halo;
R_7 is hydrogen, halo, methyl or trifluoromethyl; **and**
R_8 is hydrogen or halo**[;**
R_{16} is chosen from di(lower alkylamino), (lower alkyl)amino, amino, N-heterocyclyl and substituted N-heterocyclyl].

18. (Twice Amended) A method according to claim 1 wherein
R_1 is benzyl or halobenzyl;

R_2 is chosen from ethyl and propyl;

R_2' is hydrogen;

R_3 is substituted phenyl;

[$R_{3'}$ is substituted phenyl;

$R_{3''}$ is substituted phenyl;]

R_4 is $(CH_2)_m OH$ or $(CH_2)_p R_{16}$ wherein m is 2 or 3 and p is 1-3;

R_5 is hydrogen;

R_6 is hydrogen;

R_7 is halo;

R_8 is hydrogen;

R_{16} is chosen from amino, propylamino, and azetidinyl.